

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

22201 23rd Drive SE
Bothell, WA 98021-4421
(425) 486-8788 Fax: (425) 483-4996

DATE(S) OF INSPECTION

03/31/2008 - 04/09/2008*

FEI NUMBER

3003294857

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Lawrence A. Newman,, Technical Executive

FIRM NAME

Kirkman Group Inc., DBA Kirkman
Laboratories Inc.

STREET ADDRESS

6400 Rosewood St

CITY, STATE, ZIP CODE, COUNTRY

Lake Oswego, OR 97035-5392

TYPE ESTABLISHMENT INSPECTED

Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

QUALITY CONTROL SYSTEM

The Quality Unit has failed to meet its responsibilities in that:

OBSERVATION 1

Written records of investigation of a drug complaint do not include the findings of the investigation and the follow-up.

Specifically,

For example, there were three complaints reported in the Year 2007 related to prescription fluoride drug products. The SOP, Section Thirty-Nine: Quality Control Responsibilities and Authority Item 7 states that QC shall maintain, review and evaluate all customer complaints as part of the corporate complaint file, however,

A. A complaint was received on 2/2/07 through the Purchasing Department regarding bottles of Fluoride returned with "strange black spots on them". There was no review, follow-up or corrective/preventative action documented by Quality Control.

B. A complaint was received on 4/20/07 through the Purchasing Department regarding Perry Fluorabon Drops with "black particulate matter floating in the product". There was no review, follow-up or corrective/preventative action documented by Quality Control.

C. A complaint was received on 12/17/07 through the Purchasing Department regarding Sodium Fluoride Tablets (Lot Numbers 063477 and 063478) regarding tablets with brown spots and irregular color. There is no review, follow-up or corrective/ preventative action documented by Quality Control.

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[Inadequate Complaint Investigation is a repeat FDA-483 Observation]

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically, SOP Section Thirty-Nine: Quality Control Responsibilities and Authority states that QC shall evaluate any deviations or changes noted during the manufacturing or packaging of a product. However, following is an example of deviations in the manufacturing, packaging, and in process testing that have not been evaluated by QC:

A. The one year laboratory stability testing results (dated 4/3/06) of Kirkman Flura-Drops USP, Lot 073-21 (b) (4) from (b) (4) resulted in a 140% yield (7000 mg/L) of fluoride. The established USP limits are 90% -110%. The firm sent the same product to a different laboratory, (b) (4) on 8/23/06 (4.5 months later) and the test results of the Kirkman Flura-Drops USP, Lot 073-21, Exp. 02/07 were reported as 107% yield/serving of fluoride. There was no documented investigation/corrective action as to the initial out of specification fluoride result and/or discrepancy of the results between the two laboratories.

B. Laboratory testing of Kirkman Flura Drops ½ strength, Lot 221-5 Exp. 04/08 resulted in a 110.2% yield/serving of fluoride. This is outside the USP limits of 90% - 110%. No documented investigation with corrective actions was initiated.

C. Numerous observations were noted in the Packaging Master records for Perry Fluorabon Drops USP (Item 072) and Flura-Drops (Item 073). There was no documented evaluation performed by QC. For example,

- As it relates Fluorabon Drops USP (Product Number MP072):

Date Packaged	Lot Number	Deviation
1/31/06	072-15/0131	Eight tips destroyed due to illegible printing of 30 mL line on dropper. Two bottles destroyed due to pink tint inside of the bottle. Label printing deviations.

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6/1/06	072-17/0601	Eleven bottles destroyed. Found a bug in Box Lot 1171. Lid would not tighten on bottle.
11/7/07	072-022/1107	Puncture hole in tip of dropper.
1/16/08	072-022/0116	Labels illegible. Packaging boxes smearing. Purchasing aware.
3/7/08	072-023/0307	One bottle had a black spot. Lot number illegible on the label.
3/10/08	072-023/0310	Four bottles had black spots. Purchasing aware.

2. As it relates to Flura-Drops (MP073):

Date Packaged	Lot Number	Deviation
12/14/07	073-031/1214	Two bottles had pink stuff inside. Two bottles had deformed threads on top.
1/2/08	073-032/0102	One bottle discolored. One white cap had a black spot.
1/23/08	073-032/0123	Threading on top of bottles faulty. Purchasing aware.
1/28/08	073-032/0129	Three bottles have problems with top threads. Purchasing aware.
2/1/08	073-032/0201	One bottle had problems with the top threads. Purchasing aware.
2/27/08	073-032/0227	White caps have black spots. Purchasing aware.
3/3/08	073-032/0303	Tips have spots and look dirty. Purchasing aware.
3/17/08	073-033/0317	Bottle bubbled in the shrink machine. Technical Executive of manufacturing (not QC) stated that "it's OK for fluoride liquid to get hot."

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[Inadequate discrepancy evaluations is a repeat FDA-483 Observation]

OBSERVATION 3

The master production and control records are deficient in that they do not include complete manufacturing, control, instructions, sampling, testing, procedures, and specifications.

Specifically,

QC is responsible for the final check for accuracy of the Master Formula for fluoride drug products (SOP Section Five); however, critical steps in the pediatric liquid fluoride manufacturing operation are not documented. For example,

A. The Manufacturing Team Leader, stated that during the manufacture of the Fluorabon Drops and Flura Drops, in order to determine that all ingredients are adequately mixed, (b) (4) of solution are removed and checked for clarity. This step is not documented in the Manufacturing Formula Specification Sheet. The solution is returned to the mixing tank after the clarity has been assessed.

B. As per the Manufacturing Team Leader, (b) (4) is used to filter the liquid fluoride drug product from the mixing vessel into the (b) (4) jugs. The use of the (b) (4) is not documented in the Fluorabon Drops (List #MP072).

C. Distilled water is to be heated to (b) (4) degrees C prior to the addition of (b) (4). The solution is to be cooled to (b) (4) degrees C; however, the temperatures are not recorded in the Manufacturing Formula Specification Sheet.

D. The final liquid fluoride drug product is to be mixed "well" for (b) (4) minutes; however the mixing time is not recorded.

E. A complete list of equipment used in the fluoride liquid drug product manufacture is not listed on the Manufacturing Formula Specification Sheet. For example, the balances/scales/graduated cylinder used to weigh the raw ingredients; the type of thermometer; and the mixing container used in the manufacture of the half-strength Flura Drops are not recorded on the Manufacturing Formula Specification Sheet.

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OBSERVATION 4

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

For example,

- A. There is no established change control system.
- B. SOP Section Thirty-Nine: Quality Control Responsibilities and Authority Item 2 states that QC shall approve or reject all procedures. However, the Packaging Master Control records are not approved/controlled by QC. Handwritten procedures are used by the Packaging Department to package and label finished dose drug product for distribution. These procedures have not been approved by QC.
- C. As per SOP Section Three – Assignment of lot codes for raw materials, manufactured products, bought out products and components, raw materials and components are to be given a sequential receipt number upon receipt. However, the firm's current procedure is to assign the purchase order number to the raw materials/components rather than a sequential receipt number.

OBSERVATION 5

Individuals responsible for supervising the manufacture, processing, packing, and holding of a drug product lack the training to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess.

Specifically, the Quality Control Team Leader, the Manufacturing Technical Executive/Group Leader of Production, and the Manufacturing Team Leader, who are responsible for training employees in GMPs related to the manufacture of drug products have received no formal documented training in cGMPs.

PRODUCTION/EQUIPMENT SYSTEMS

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OBSERVATION 6

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically, your firm has not performed process validation and critical manufacturing equipment has not been qualified. For example,

- A. The machine tooled gauges that are used to measure the amount of distilled water (gallons) added into the formula initially and to Q.S. to the final measurement based on batch size have not been qualified.
- B. Appropriate weights are not being used to validate the performance of the test range being used on the (b) (4) Balance # (b) (4). For example, Balance # (b) (4) which has a test range from (b) (4) grams (g) is being used to weigh (b) (4) g of Sodium Fluoride USP for Flura Drops (List Number MP073). According to the "CHECK SCALE CALIBRATION LOG SCALE # (b) (4)" dated 4/3/08 a (b) (4) g test weight is being used to validate the performance of this balance. There has been no qualification of the upper test range of this balance.
- C. The (b) (4) Balance # (b) (4) is used as a portable balance. There is no procedure established to assure that the balance is leveled prior to use. The scale has not been qualified for its intended use.
- D. The (b) (4) gram test weight used to check calibration of Balance # (b) (4) and Balance # (b) (4) prior to use in the manufacture of fluoride drug products is not stored and/or handled in a manner to prevent possible damage.
- E. A non-qualified thermometer is used to measure the temperature during the manufacture of the Fluorabon Drops and Flura Drops.
- F. There has been no determination that the (b) (4) used to filter the final solution of Fluorabon Drops and Flura Drops is not additive.

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OBSERVATION 7

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, a cleaning validation has not been performed for equipment used in the prescription fluoride manufacturing operation. Equipment maintenance is not documented. The Standard Operating Procedures (SOP) Section Ten states: Secondary equipment used in manufacturing, describes that equipment is to be cleaned; however there is no direction as to what should be cleaned and the methods of cleaning. Section Twelve of the SOP: Cleaning procedures for manufacturing equipment states that "Equipment used for drug (sodium fluoride) products will be cleaned with water only"; however, there is no direction as to what should be cleaned and the methods of cleaning.

For example,

- A. There is no cleaning procedure for the Model (b) (4) pump and tubing used to extract water out of (b) (4) drums for use in the manufacture of the prescription pediatric fluoride drop drug products. The pump and tubing are stored in a plastic bag and standing water was observed in the tubing during this inspection. The pump and tubing have been used for "many years", per the Manufacturing Team Leader, without documented cleaning/maintenance. Yellow droplets of an unknown liquid were also observed in the plastic bag used to store the pump and tubing.
- B. There is no cleaning procedure for the (b) (4) tank used in the manufacture of the pediatric fluoride drop drug products. Standing water was observed during this inspection in the piping used to deliver manufactured drug product from the (b) (4) tank to the (b) (4) storage jugs.
- C. There is no cleaning/maintenance procedure for the pumps used to transfer pediatric fluoride drug products from (b) (4) jugs to final packaging containers. Pumps were observed stored unprotected in a drawer in an open plastic bag with a paper towel used to absorb excess moisture. The pump is wrapped with tape to aid in metering the correct fill amount; however there is no documentation that the tape is cleaned and/or changed after each use.
- D. There is no procedure to clean the top of (b) (4) barrels, prior to insertion of the distilled water pump through the threaded caps, in order to prevent possible contamination. The barrels and caps were observed to be dirty during this inspection.

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[Lack of cleaning validation is a repeat FDA-483 Observation]

LABORATORY CONTROL SYSTEM

OBSERVATION 8

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

For example,

A. Testing to verify the identity and strength of the active ingredient, sodium fluoride, is not performed on the pediatric full-strength FLURA-DROPS, half-strength FLURA-DROPS, and Perry Medical Fluorabon Drops USP prior to release. Testing for the active ingredient, sodium fluoride, is performed on the in-process bulk drug product when it is filled into the (b) (4) storage jugs; however, these jugs can be stored up to (b) (4) before the bulk drug product is transferred to the final packaging (final dosage form) and released for distribution.

B. Laboratory analysis used to determine the sodium fluoride content of Fluorabon Drops USP in terms of the content of fluoride ion was not performed by a laboratory using a USP method prior to 8/23/2006. There was no determination based on scientific rationale that the method used by the laboratory was comparable to the USP method.

C. As per the USP, Sodium Fluoride Oral Solution is listed as having a pH below 7.5; however, the pH of Fluorabon Drops USP is not tested and was unknown as of the start of this inspection.

D. There was an early release for Flura-Drops Lot Numbers 073-30/0824 and 073-27/0108. Flura-Drop Lot #073-30 was packaged on 8/24/07. As documented on the Packaging Master Record dated 8/24/07, there was an early release of (b) bottles (Lot #073-30/0824) on 9/4/07 "so an order can go out". Quality Control did not sign the Final Release form until 9/5/07. On 1/8/07 there was an early release of (b) bottles (Lot #073-27/0108) documented on a piece of paper included with the packaging record. Quality Control did not sign the Final Release form until 1/10/07.

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OBSERVATION 9

Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically, Fluorabon Drops USP and Flura-Drops are transferred from a (b) (4) mixing vessel into (b) (4) jugs for bulk storage. The (b) (4) jugs can be held up to (b) (4) of the three year expiration date prior to packaging in the final dosage bottles. No stability study has been performed to assure the quality of the pediatric fluoride drug product stored in the (b) (4) jugs.

OBSERVATION 10

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.

Specifically, Methyl and Propyl Paraben (preservatives) are added into the Flura Drops and Fluorabon Drops. However there is no laboratory testing procedure established to assure that the preservatives are adequately formulated/tested at the time of release and/or active over the shelf life of the product.

OBSERVATION 11

The written stability testing program is not followed.

Specifically,

A. The (b) (4) stability testing for Perry Flura Drops MP072, Lot # 072-12, scheduled for 7/30/07, was not performed.

B. The (b) (4) stability testing for Kirkman Flura Drops MP073, Lot # 073-21, scheduled for 8/23/07 was not performed.

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OBSERVATION 12

The written stability program for drug products does not describe the storage conditions for samples retained for testing.

Specifically, no thermometer or other device is used to record and monitor the storage conditions of the stability cabinet.

OBSERVATION 13

The written stability program does not assure testing of the drug product in the same container-closure system as that in which the drug product is marketed.

Specifically,

The firm has not performed stability testing on the prescription fluoride tablets in the container/closure system used to market the following products: 674- 1.1 Grape Tablets, 675- 0.55 Lemon Tablets, and 76- 2.21 Cherry Tablets. The fluoride table supplier provided a Certificate Of Analysis in lieu of stability testing. However, the testing was performed in a (b) (4) bottle with (b) (4) liner and your firm currently uses a (b) (4) and (b) (4) bottle with (b) (4) liner.

MATERIAL SYSTEM

OBSERVATION 14

The identity of each component of a drug product is not verified by conducting at least one test to verify the identity, using specific identity tests if they exist.

For example,

A. Distilled Water (Item #R276) used in the manufacture of pediatric liquid prescription fluoride drug products is delivered from an outside vendor in (b) (4) drums. There is no testing performed and there is no documentation as to the microbiological and chemical quality of the water prior to release for manufacturing in the fluoride drug product manufacturing operation.

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B. Industrial grade (b) (4) is used (b) (4) for liquid prescription drug products that are stored in (b) (4) jugs prior to packaging. There is no certificate of analysis and there has been no verification that the (b) (4) used is suitable for use in a drug manufacturing operation. The lot number of the (b) (4) is not recorded in the Manufacturing Formulation Specification Sheet.

C. No testing has been performed and/or is performed to confirm that the tips and droppers used to deliver a pediatric dose of sodium fluoride, as purported on the package labeling, are accurate. Four drops of Flura-Drops are purported to contain 2.21 mg of sodium fluoride. Fluorabon Drops USP are purported to contain 0.25 mg of Fluoride Ion in 0.6 ml of solution.

D. Release of material specifications have not been established for cotton balls purchased from local retail businesses and cotton coil used in the packaging operation of prescription fluoride tablets. No identity testing is currently performed by quality control prior to release of these items for use in the prescription fluoride manufacturing operation.

OBSERVATION 15

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each component and establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically, one specific test is not performed on each component of your prescription drug products including the following components: Methyl Paraben (Item #R140), Propyl Paraben (Item #R141), Sodium Fluoride USP (R142), and (b) (4) (Item #R189).

FACILITIES

OBSERVATION 16

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically, the floors in the Liquid Fluoride Manufacturing Room were observed to be cracked and chipping.

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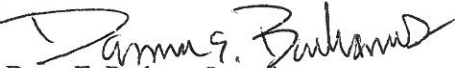
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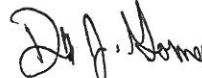
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03/31/2008(Mon), 04/01/2008(Tue), 04/02/2008(Wed), 04/03/2008(Thu), 04/04/2008(Fri), 04/09/2008(Wed)

FDA EMPLOYEES' NAMES, TITLES, AND SIGNATURES:


Dawn E. Barkans, Investigator


David J. Gomes, Analyst

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